IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 09/822,716	Confirmation No.: 7248
Applicant	: David A. Edwards and Jeffrey S. Hrkach	
Filed	: March 30, 2001	
TC/A.U.	: 1616	
Examiner	: Mina Haghighatian	
Docket No.	: 2685.1003-008 (US3)	
Customer No.	: 000038421	
Title	: PARTICLES FOR INHALATION HAVING SUSTAINED RELEASE PROPERTIES	

CERTIFICATE OF MAILING

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APPEAL BRIEF

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Sir:

This Brief is being filed pursuant to 37 CFR 1.192, all claims having been more than twice rejected. The Notice of Appeal and requisite fee were filed on November 23, 2004. The fee for the Brief under 37 CFR 1.17(h) and request for Oral Hearing are being filed herewith.

(1) The Real Party of Interest

The real party of interest in this appeal is Advanced Inhalation Research, Inc. by virtue of the Assignment recorded on September 24, 2001, at Reel 012190 and frame 0812-0815.

(2) Related Appeals and Interferences

There are no related appeals or interferences at this time known to the appellant, the Assignee or its Representatives which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of the Claims

Claims 1-8, 10, 13-29 and 49-52 are pending, finally rejected and are appealed. Claims 9, 11, 12, 30-48 have been canceled.

(4) Status of Amendments

An Amendment After Final Rejection was filed on September 16, 2004 and entered by the Examiner.

(5) Summary of the Invention

The invention relates to a method of delivery to the pulmonary system comprising: the steps of administering to the respiratory tract of a patient in need of treatment, prophylaxis or diagnosis an effective amount of a dry powder comprising:

a) a multivalent metal cation which is complexed with a therapeutic, prophylactic or diagnostic agent;
b) a pharmaceutically acceptable carrier; and
c) optionally, a multivalent metal cation-containing component.

The dry powder is spray-dried and has a total amount of multivalent metal cation which is more than about 1% w/w of the total weight of the agent, a tap density of

less than about 0.4 g/cm^3, a median geometric diameter of between about 5 micrometers and about 30 micrometers and an aerodynamic diameter of from about 1 to about 5 microns.

(6) Issues

The first issue on appeal is whether the Examiner has established a *prima facie* case of obviousness under 35 U.S.C. 103 over Jensen in view of Maa, over Jensen in view of Weers, and over Jensen in view of Weers, further in view of the International Ingredient Dictionary and Handbook.

(7) Grouping of Claims

The claims stand and fall together.

(8) Argument

The Examiner has rejected claims 1-10, 12-17, 21-26, 28, 49, and 51-52 under 35 U.S.C. §103(a) as being unpatentable over Jensen in view of Maa et al. (U.S. Pat. No. 6,284,282, "Maa"). The Examiner states that Jensen lacks specific disclosure on tap density of the powder particles. The Examiner states that Maa discloses a method of freeze spray drying proteins for pharmaceutical administration, and that the protein particles of Maa have a tap density of less than about 0.8g/cm^3, with a tap density of less than about 0.4g/cm^3 being preferred. The Examiner also states that Maa discloses proteins which include insulin. The Examiner concludes that it would have been obvious to a person of ordinary skill in the art at the time the invention was made given the general teachings of powder formulation of insulin of Jensen to have looked in the art for specific particle characteristics such as tap density as disclosed by Maa et al, with reasonable expectations of preparing effective formulations for pulmonary delivery by improving their dispersibility, absorbability and respirability. Appellants respectfully disagree with the Examiner's conclusion.

Jensen states that the invention disclosed therein is directed towards a method of producing a therapeutic powder formulation by a process involving precipitation of an

aqueous solution comprising insulin and an enhancer to produce a powder formulation (see, column 2, lines 41-54). Jensen states that the ability to precipitate insulin and an enhancer is surprising because the enhancer normally inhibits precipitation (see, column 2, lines 36-40). Jensen also states that the powder formulation produced by the process disclosed therein has enhanced features, such as stability and flowability, as compared to the same formulation produced by spray drying, freeze spray drying, vacuum drying and open drying. Jensen further states that the process of the invention disclosed therein is preferably carried out so as to obtain a substantially crystalline product (see, column 4, lines 4-8).

Jensen's disclosure of a process for preparing a formulation by precipitation teaches away from the presently claimed invention. Jensen specifically states that that the powders resulting from the precipitation process described therein are different from, and provide advantages over, similar compositions that have been spray dried or freeze dried. In other words, Jensen himself teaches that the products possess the properties described therein because of the process used to produce the products. Applicants have amended the instant claims to recite additional features that the powder compositions of the instant invention comprise, such as tap densities of less than 0.4 g/cm^3, aerodynamic diameters of from about 1 to about 5 microns and particle sizes of about 5 to about 30 microns. The ability to control the range of the tap density, aerodynamic diameter and particle size of powders of the invention relies on the spray-drying process by which the powder compositions of the present invention are produced. In contrast, Jensen's disclosed precipitation process does not provide a means for controlling or achieving the tap density, aerodynamic size or average particle size of the powder formulations resulting from the precipitation process. The precipitation process disclosed by Jensen yields crystals. These crystals are the result of allowing a spontaneous amorphous precipitate to rest for a period of time to allow the formation of crystals which are then dried to form the dry powder disclosed therein. The crystals resulting from the precipitation process described by Jensen are whatever size and shape that the precipitation process yields. Jensen does no more than measure the size of the resulting crystals. One skilled in the art would not look to a precipitation process such as that

disclosed by Jensen, if the skilled practitioner was concerned about controlling the tap density, aerodynamic diameter and particle size of the final powder product as is presently claimed.

Similarly, Jensen teaches away from Maa. Maa discloses that the desired tap density, aerodynamic diameter and geometric diameters of particles disclosed therein may be achieved by freeze spray drying, and that particles having such specified characteristics can be achieved through manipulation of certain parameters of the freeze spray drying procedure (see Maa, column 4, line 60 to column 5 line 29). As Jensen discloses a fundamentally different process that teaches away from the formulations produced by freeze spray drying disclosed in Maa, there is no motivation to combine Jensen with Maa as the Examiner has done (*Tec Air, Inc. v. Denso Manufacturing Michigan Inc.*, 192 F.3d 1353, 1360, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999) ("There is no suggestion to combine ... if a reference teaches away from its combination with another source")). Even if one were motivated by Maa to prepare particles having the listed properties, Maa does not teach how one would accomplish this goal using the process of Jensen.

The Examiner dismisses these arguments, stating that the method of manufacturing the product is not relevant. This is untrue. It is agreed that where the product produced by one process is the same as or obvious over a product produced by a different process, the process limitations do not render patentability to the product. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). However, where the record establishes that the products produced by the two processes differ, then the process can impart patentable features. For example, where the product can only be defined by the process steps or the process steps impart distinctive characteristics on the product, the process limitations should be considered. *In re Garnero*, 162 USPQ 221 (CCPA 1979). Thus, the Examiner can only properly "ignore" the process limitations where the process is not expected to have a substantive impact upon the product. Where, as here, the evidence suggests that the process has a substantive impact on the product, the limitations cannot be ignored. It is urged that these holdings apply even where the claims are directed to methods of using the product, as compared to the product itself.

The claims require that the product be spray dried. See the "wherein" clause of Claim 1, for example. As discussed above, this limitation cannot be ignored simply because the preamble of the claim is directed to a method by which these compositions are used. The method of preparing the composition can have substantial effects on the products. For example, Jensen uses a precipitation method to achieve his product. Jensen characterizes the method of manufacture as being a ***critical*** element for its success in achieving a product that can be used for pulmonary delivery. Jensen does not teach that the method of manufacturing can be ignored with respect to obtaining a successful product. Indeed, a product must be made before it can be administered. It is not an inseparable part of the method of use. Jensen simply teaches away from spray drying products for pulmonary delivery. A claim which is limited to spray-dried products is not taught or made obvious by Jensen's teachings. The Examiner cannot properly ignore this limitation in the claim.

The Examiner states that "All that is required to meet the limitations of claim 1 is a method of delivering to the pulmonary system a powder comprising a multivalent cation, an active agent and a carrier." This is untrue. The Examiner must provide a teaching in the prior art for each and every limitation in Claim 1, not just those cited by the Examiner in this sentence. The Examiner is improperly ignoring limitations which appear in the claims. These limitations include the spray-drying limitation discussed above. The limitations also include the physical characteristics listed in the wherein clause and the relative amounts of excipients in Claim 1. The Examiner cannot properly ignore these limitations.

The Examiner dismisses Appellants' arguments that the references cannot be properly combined, "because Jensen teaches delivery of powders to the pulmonary system successfully." While it is true that Jensen teaches delivery of powders to the pulmonary system, one cannot ignore the teachings of the references. Both references critically rely upon the processes which are used to produce a product that can be delivered successfully. There is no reason provided by the Examiner to mix and match components of these two very different processes with an expectation that the resulting product could be successfully delivered. Indeed, the physical characteristics of the

product are derived from the process by which they are produced. Both of these references acknowledge that fact. Jensen, for example, states that the products that are produced are different than those made by using spray drying and freeze drying techniques (see column 2, lines 55-64). One simply would not look to the teachings of Maa to modify the Jensen process or make modified products for pulmonary delivery.

Again, in considering whether or not the references are properly combined, Examiner ignores the processes by which the products are made in the references because the claims are directed to the method of using products or the products themselves. This is improper. The products must be made before they can be delivered. Where the references rely upon the method by which the products are made to achieve products suitable for delivery, those processes cannot be ignored. Both references acknowledge that different processes achieve different products. Thus, referencing the preamble of the present claims to determine whether or not it is proper to ignore teachings of the references and combine the references, in spite of those teachings, is clearly improper.

The Examiner acknowledges that Jensen does not teach the properties of the particles that it produces. That is true. However, it does not follow that one of ordinary skill in the art would expect these particles to possess characteristics of the preferred particles of Maa or that one would be motivated, with an expectation of success, to make such particles. Given the absence of this teaching in Jensen and the declared success by using the described process of Jensen, one would not be motivated to turn to Maa to select these physical characteristics and then modify the process of Jensen to achieve these characteristics with a reasonable expectation of success without undue experimentation.

In the Advisory Action, the Examiner asserts that the "wherein" clause and metal cation-containing component of (c) are optional. While it is true that the metal cation-containing component of (c) is optional, the metal cation complexed to the agent is not. See paragraph (a). With respect to the "wherein" clause, Appellants disagree that this limitation is optional. Claim 1, as originally formatted provided the wherein clause in a separate subparagraph as the ingredients of the particles in subparagraphs (a)-(c). If the

unintentional reformatting in the Amendment After Final Rejection caused confusion, the undersigned apologizes to the Office.

The Examiner has rejected claims 1-17, 21-28, 30-40, 44-52 under 35 U.S.C. §103(a) as being unpatentable over Jensen in view of Weers et al. (6,309,623). The Examiner states that Jensen lacks the specific disclosure of tap density and geometric diameter of the insulin particles. The Examiner states that Weers teaches stabilized preparations for the delivery of a bioactive agent to the respiratory tract of a patient using a metered dose inhaler. The Examiner further states the particles disclosed in Weers have a mean geometric diameter of less than 20 micrometers or less than 10 micrometers and most preferably less than about 5 micrometers. The Examiner also states that Weers teaches that the particles have a tap density of less than 0.5 g/cm^3 , a mean aerodynamic diameter of less than about 3 micrometers and the particle preparations are suitable for deep lung delivery. Finally, the Examiner states that Weers also discloses inhalation formulations that include insulin. The Examiner concludes that it would have been obvious to a person of ordinary skill in the art at the time the invention was made given the general teachings of powder formulation of insulin of Jensen to have looked in the art for specific particle characteristics such as tap density as disclosed by Weers et al., with reasonable expectations of preparing effective formulations for pulmonary delivery by improving their dispersibility, absorbability and respirability. Appellants respectfully disagree with the Examiner's conclusion.

As with the Examiner's combination of Jensen and Maa above, Jensen teaches away from the stabilized preparations disclosed in Weers. As discussed above, Jensen's dry powders are produced by a precipitation process that results in dry powders that are mostly crystalline particles. Jensen specifically states that that the powders resulting from the precipitation process described therein are different from, and provide advantages over, similar compositions that have been spray dried or freeze dried.

In contrast, Weers discloses that the stabilized preparations described therein are the result of the use of hollow and/or porous perforated microstructures having particular characteristics such as specific tap densities, aerodynamic size and geometric diameters

(see Weers, column 4, lines 5-10, all of columns 13 and 14). The crystalline particles resulting from the precipitation process disclosed by Jensen are relatively dense, solid and non-porous as compared to the hollow and/or porous perforated microstructures of Weers. Weers further discloses that the hollow and/or porous perforated microstructures disclosed therein are the result of a process that provides control over a number of parameters to allow for the formation of such hollow, and/or porous perforated microstructures (see column 22, lines 12-32) comprising the desired tap density, aerodynamic diameter and geometric diameters. Examples of suitable processes disclosed by Weers include spray drying (column 21, lines 12-22) or freeze drying (lyophilization) (column 25, lines 62-column 26, line 18) of microparticle reagents, or certain emulsion procedures (column 26, lines 18- 33). A precipitation process such as that disclosed in Jensen does not, by its nature, provide one skilled in the art with the means to control the formation of the crystals from the precipitate such that the resulting crystals are hollow and/or porous and possess desired tap density, aerodynamic and geometric sizes of the stabilized formulations of Weers.

Therefore, one skilled in the art would not be motivated to combine Jensen and Weers, as Jensen teaches away from a process and a product such as that described in Weers.

The Examiner dismisses these arguments for the reasons set forth above with respect to Jensen and Maa, discussed above. For all the reasons set forth above, the Examiner is in error.

The Examiner has rejected claims 18-20, 29 and 41-43 under 35 U.S.C. §103(a) as being unpatentable over Jensen in view of Weers further in view of the International Ingredient Dictionary and Handbook. The Examiner states that Jensen lacks specific disclosure on the inclusion of carboxylic acid in the formulation, but that Jensen teaches that hydrochloric acid is added to the formulation to adjust the pH. The Examiner asserts that the International Ingredient Dictionary and Handbook discloses that carboxylic acids such as citric acids are well known pH adjusters in pharmaceutical formulations. The Examiner concludes that one skilled in the art would have been motivated to replace hydrochloric acid of Jensen with citric acid to perform a pH adjusting function and that

the expected result would be a successful formulation for the pulmonary delivery of insulin.

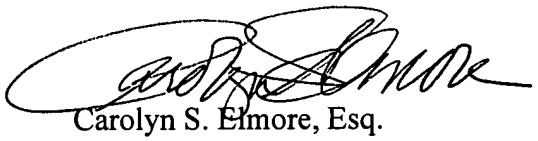
In response, Applicants respectfully submit that the combination of Jensen, Weers and the International Ingredient Dictionary and Handbook does not make obvious the presently claimed invention. The International Ingredient Dictionary and Handbook does not provide what the Jensen and Weers references lack. Accordingly, applicants respectfully request that the rejection of the claims in view of the combination of Jensen and the International Ingredient Dictionary and Handbook be withdrawn.

Reversal of the rejections is requested.

(9) Conclusion

Appellants again request reversal of the rejections and the allowance of the application.

Respectfully submitted,



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PENDING CLAIMS

1. (Previously Amended) A method of delivery to the pulmonary system comprising:
administering to the respiratory tract of a patient in need of treatment, prophylaxis or diagnosis an effective amount of a dry powder comprising:
a) a multivalent metal cation which is complexed with a therapeutic, prophylactic or diagnostic agent;
b) a pharmaceutically acceptable carrier; and
c) optionally, a multivalent metal cation-containing component
wherein, the dry powder is spray-dried and has a total amount of multivalent metal cation which is more than about 1% w/w of the total weight of the agent, a tap density of less than about 0.4 g/cm^3, a median geometric diameter of between about 5 micrometers and about 30 micrometers and an aerodynamic diameter of from about 1 to about 5 microns.

2. (Original) The method of Claim 1, wherein the biologically active agent is a protein.

3. (Original) The method of Claim 2, wherein the protein is insulin.

4. (Original) The method of Claim 2, wherein the multivalent metal cation is selected from Zn(II), Ca(II), Cu(II), Ni(II), Co(II), Fe(II), Ag(II), Mn(II), Mg(II) or Cd(II).

5. (Original) The method of Claim 4, wherein the multivalent metal cation is Zn(II).

6. (Original) The method of Claim 2, wherein the multivalent metal cation is present at a ratio of more than about 2% w/w of the total weight of the agent.

7. (Original) The method of Claim 2, wherein the multivalent metal cation is present at a ratio of more than about 5% w/w of the total weight of the agent.

8. (Original) The method of Claim 2, wherein complexation of the agent and multivalent metal cation comprises a metal coordination.

9. (Canceled)

10. (Previously Amended) The method of Claim 2, wherein the dry powder has a tap density less than about 0.1 g/cm^3.

11. (Canceled)

12. (Canceled)

13. (Previously Amended) The method of Claim 2, wherein the dry powder has an aerodynamic diameter of from about 1 to about 3 microns.

14. (Previously Amended) The method of Claim 2, wherein the dry powder has an aerodynamic diameter of from about 3 to about 5 microns.

15. (Original) The method of Claim 2, wherein delivery to the pulmonary system includes delivery to the deep lung.

16. (Original) The method of Claim 2, wherein delivery to the pulmonary system includes delivery to the central airways.

17. (Original) The method of Claim 2, wherein delivery to the pulmonary system includes delivery to the upper airways.

18. (Original) The method of Claim 2, wherein the dry powder further comprise a carboxylic acid.

19. (Original) The method of Claim 18, wherein the carboxylic acid includes at least two carboxyl groups.

20. (Original) The method of Claim 19, wherein the carboxylic acid is citric acid or a salt thereof.

21. (Original) The method of Claim 2, wherein the dry powder further comprise an amino acid.

22. (Original) The method of Claim 21, wherein the amino acid is hydrophobic.

23. (Original) The method of Claim 22, wherein the hydrophobic amino acid is leucine, isoleucine, alanine, valine, phenylalanine or any combination thereof.

24. (Original) The method of Claim 2 wherein the pharmaceutically acceptable carrier is a phospholipid.

25. (Original) The method of Claim 24 wherein the phospholipid is a phosphatidic acid, a phosphatidylcholine, a phosphatidylalkanolamine, a phosphatidylethanolamine, a phosphatidylglycerol, a phosphatidylserine, a phosphatidylinositol or combinations thereof.

26. (Previously Amended) A method of delivery to the pulmonary system comprising:

administering to the respiratory tract of a patient in need of treatment, prophylaxis or diagnosis an effective amount of a dry powder comprising:

a) a protein which is complexed with zinc;

b) a pharmaceutically acceptable carrier; and

c) optionally, a multivalent metal cation-containing component wherein, the dry powder is spray-dried and has a total amount of multivalent metal cation which is more than about 2 % w/w of the total weight of the agent, a tap density of less than about 0.4 g/cm^3, a median geometric diameter of between about 5 micrometers and about 30 micrometers and an aerodynamic diameter of from about 1 to about 5 microns.

27. (Previously Amended) The method of Claim 26, wherein the dry powder has a tap density less than about 0.1g/cm^3.

28. (Original) The method of Claim 26, wherein the pharmaceutically acceptable carrier is a phospholipid.

29. (Original) The method of Claim 26 wherein the dry powder further comprises a carboxylic acid.

30-48. Canceled.

49. (Previously Amended) A composition for delivery to the pulmonary system comprising:

administering to the respiratory tract of a patient in need of treatment, prophylaxis or diagnosis an effective amount of a dry powder comprising:

a) a protein which is complexed with zinc;

b) a pharmaceutically acceptable carrier; and

c) optionally, a multivalent metal cation-containing component

wherein, the dry powder is spray-dried and has a total amount of multivalent metal cation which is more than about 2 % w/w of the total weight of the agent, a tap density of less than about 0.4 g/cm^3, a median geometric diameter of between about 5 micrometers and about 30 micrometers and an aerodynamic diameter of from about 1 to about 5 microns.

50. (Previously Amended) The method of Claim 49, wherein the dry powder has a tap density less than about 0.1g/cm^3.

51. (Original) The method of Claim 49, wherein the pharmaceutically acceptable carrier is a phospholipid.

52. (Original) The method of Claim 49 wherein the dry powder further comprises a carboxylic acid.